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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/618,856

07/15/2003

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SOLOMON=2A.1

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EXAMINER

BALLARD, KIMBERLY A

ART UNIT	PAPER NUMBER
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1649

MAIL DATE	DELIVERY MODE
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06/04/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

<p align="center">Office Action Summary</p>	<p>Application No.</p> <p align="center">10/618,856</p>	<p>Applicant(s)</p> <p align="center">SOLOMON ET AL.</p>	
	<p>Examiner</p> <p align="center">Kimberly A. Ballard</p>	<p>Art Unit</p> <p align="center">1649</p>	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 08 March 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-12 and 18 is/are pending in the application.
- 4a) Of the above claim(s) 9 and 11 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-8, 10, 12 and 18 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

RESPONSE TO AMENDMENT

Claim 18 has been added as requested in the amendment filed March 8, 2007.

Following the amendment, claims 1-12 and 18 are pending in the current application.

Claims 9 and 11 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on October 19, 2005. Accordingly, claims **1-8, 10, 12 and 18** are under examination in the instant office action.

The Examiner of U.S. Patent Application No. 10/618,856 has changed. In order to expedite the correlation of papers with the application, please direct all future correspondence to Examiner Ballard, Technology Center 1600, Art Unit 1649.

Withdrawn Claim Rejections

Applicants' arguments, see page 9 of the response filed March 8, 2007, with respect to the rejection of claims 1, 8 and 12 under 35 U.S.C. 102(a) and (e) have been fully considered and are persuasive. The rejection of claims 1, 8 and 12 under 35 U.S.C. 102 (a) and (e), as set forth at ¶¶11-12 of the previous office action mailed 09/08/2006, has been withdrawn.

Applicants' arguments, see page 12 of the response filed March 8, 2007, with respect to the rejection of claims 1-8, 10 and 12 under 35 U.S.C. 103(a) have been fully considered and are persuasive. The rejection of claims 1-8, 10 and 12 under 35 U.S.C. 103(a), as set forth at ¶15 of the previous office action mailed 09/08/2006, has been withdrawn.

Maintained Claim Rejections

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

The provisional rejection of claims 1-8, 10 and 12 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-20, especially claims 11-13 and 17-20, of copending Application No. 11/073,526 is

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maintained and held in abeyance until such time that allowable subject matter is identified.

In the response filed March 8, 2007, Applicants continue to request that the rejection be held in abeyance until such time that a notice of allowance is issued. No comments as to the correctness of the rejection have been noted.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The rejection of claims 1-8, 10 and 12 under 35 U.S.C. 103(a) as being unpatentable over Schenk et al. WO 99/27944 (10 June 1999), or Schenk 6,787,139 (7 September 2004 – cumulative to WO 99/27944 priority extending to 60/067,740 (12/02/1997) and 60/080,970 (04/07/1998)), Frenkel et al. (*J Neuroimmunol*, 1998; 88: 85-90), Fanutti et al. (*SIB Biochem. Soc. Trans.* 1998; 120) and Delmastro et al. (*Vaccine*, 1997; 15(11):1276-1785), in view of Bhardwaj et al. (*J Immunol Meth*, 1995; 179:165-175) and as evidenced by Winter et al. (*Ann Rev Immunol*, 1994; 12:433-455) is maintained for reasons of record and is further applied to newly submitted claim 18.

The claims are drawn to a method for inhibiting aggregation of β -amyloid in a subject or disaggregating aggregated β -amyloid in a subject, comprising administering to the subject and effective amount of a filamentous bacteriophage which displays an epitope of β -amyloid so as to elicit antibodies against said epitope, wherein said antibodies inhibit aggregation and/or cause disaggregation of said β -amyloid aggregates. Additional claim limitations include: that the bacteriophage propagates in bacterial flora (such as *E. coli*) in said recipient (claims 2 and 3); wherein said bacteriophage is fd (claim 4) or M13 (claim 7); wherein 30 days following three doses of 10^{10} units of said bacteriophage, a titer of antibodies is above 1:50,000 in the recipient, as is determined by ELISA (claim 5); wherein the β -amyloid epitope is displayed via coat glycoprotein VIII on said bacteriophage (claim 6); wherein the bacteriophage

displays SEQ ID NO: 1 (EFRH) (claim 8) via coat glycoprotein VIII (claim 10); wherein administering is to the olfactory system of the subject(claim 12); and wherein the subject is a human and the epitope of β -amyloid is of human β -amyloid (claim 18).

In the response filed March 8, 2007, Applicants argue that Schenk does not specifically disclose administration administering filamentous bacteriophage displaying an A β -epitope as a vaccine in human therapy. Moreover, Applicants direct the Examiner's attention to paragraph [0016] of the instant specification, which demonstrates the unexpected property of long-lasting serum titer of antibodies following injection of phage-carrying epitope, and which property is not suggested by any combination of the references. Further, Applicants assert that none of the references suggest that intranasal administration of the phage is capable of bypassing the blood-brain barrier. Finally, Applicants argue that the addition of Delmastro and Fanutti do not make up for the deficiencies of Schenk, and do not suggest the unexpected results of long-lasting serum titers as demonstrated by the instant specification. Accordingly, Applicants assert that the invention as a whole would not have been obvious from the large combination of references.

Applicant's arguments have been fully considered but they are not persuasive. In response to applicant's argument that the examiner has combined an excessive number of references, reliance on a large number of references in a rejection does not, without more, weigh against the obviousness of the claimed invention. See *In re Gorman*, 933 F.2d 982, 18 USPQ2d 1885 (Fed. Cir. 1991).

Briefly, the teachings of the above references can be summarized as the following: the cumulative Schenk references disclose administration of β -amyloid (particularly human β -amyloid) immunogens to a human patient in order to generate antibodies to prevent formation of amyloid plaques or dissolve existing plaques, such as for the treatment of Alzheimer's disease. The disclosed β -amyloid epitopes comprise the instant SEQ ID NO: 1, the disclosed amounts of administered immunogens are noted to be effective to elicit high antibody titers and also to effect removal or inhibition of plaque production/deposition, and Schenk teaches that the immunogenic A β peptides are can be presented as viral or bacterial vaccine.

Frenkel indicates the suitability of the peptide sequence EFRH (i.e., the instantly claimed SEQ ID NO: 1) as an epitope for controlling A β aggregation *in vivo*.

Fanutti teaches phage-display of antigenic peptides applied to vaccine design using bacteriophage fd and gVIIIp (coat glycoprotein VIII) for expression of particular epitopes in order to stimulate immunity *in vivo* with phage particles.

Delmastro further teaches the *in vivo* administration of filamentous phage M13 for display particular peptide epitopes, via either intragastric or intranasal vaccination. Delmastro demonstrates that intranasal administration of peptide-displaying phage vaccines produced notably higher antibody titers than the intragastrically administered vaccine, wherein the antibody titers produced following immunization were greater than 1:72,900 following only three immunizations (see Figure 5 on p. 1283). Specifically, Delmastro teaches that intranasal administration "appears to be a particularly convenient and effective route of delivery, resulting in the induction of high titers of

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specific antibodies both systemically and in mucosal secretions" (p. 1283, 2nd column). It is also noted that the high antibody titers persisted for greater than 12 weeks (see Figure 5). Thus, contrary to Applicants' assertions that the instant specification's results demonstrating long-lasting antibody titers are unexpected, based upon the teachings of Delmastro and the general knowledge in the art, one of skill in the art would reasonably expect both high and long-lasting antibody titers following intranasal immunization with filamentous bacteriophage displaying a peptide epitope. Thus, the alleged unexpected results reported by Applicant are not actually unexpected, since the above references appreciated the ability of intranasally administered phage to achieve antibody titer results within the scope of the instant invention.

Additionally, in response to applicant's argument that the references fail to show certain features of applicant's invention (i.e., the ability of the intranasally administered phage to cross the blood-brain barrier), at the time of the invention was filed, it was well within the knowledge of the person of ordinary skill in the art that the noninvasive intranasal route of administration was therapeutically advantageous, particularly for the treatment of neurological diseases such as Alzheimer's disease, because of the ability of intranasally administered therapeutic agents to circumvent the blood brain barrier and directly reach the brain (see, for example, p. 281, 2nd column of Thorne et al. (*Brain Res*, 1995; 692: 278-282)). Therefore, this result is also not unexpected.

Finally, Bhardwaj et al. teach fd or M13 bacteriophage for production of antibodies, and also emphasizes the advantages of using such constructs in evaluating expression via monoclonal antibodies to the fused protein. Further, Winters et al.

disclose selecting human antibodies of desired specificity, and evidence the display of human peptides and antibody fragments on bacteriophage.

Accordingly, it would have been obvious to one of ordinary skill in the art to arrive at the claimed invention using the teachings of Schenk, Frenkel et al., Fanutti et al., and Delmastro et al., such as using the bacteriophages fd or M13 to express β -amyloid epitopes for the purpose of presenting the antigen to the immune system within the host for production of antibodies, particularly via intranasal administration. As such, instant claims 1-8, 10, 12 and 18 are rendered obvious in view of the teachings of above references.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

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extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Ballard whose telephone number is 571-272-4479. The examiner can normally be reached on Monday-Friday 9AM - 5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Elizabeth C. Kemmerer

Kimberly Ballard, Ph.D.
May 21, 2007

ELIZABETH C. KEMMERER, PH.D.
PRIMARY EXAMINER